## REMARKS

Claims 2-9, 11, and 22-25 are pending in the instant application. In view of the following remarks and the attached Declaration of Stephen R. Jaspers under 37 C.F.R. § 1.132, reconsideration of the application is respectfully requested.

**Rejections under 35 U.S.C. § 103(a)**

*Ferrara*

The Examiner rejected claims 2-5, 7-9, 11, 22, 23 and 25 under 35 U.S.C. §103(a) as allegedly unpatentable over Ferrara *et al.* (US 6,455,283, hereinafter "Ferrara"). In particular, the Examiner states, *inter alia*, that Ferrara discloses a human vascular endothelial growth factor, VEGF-E, which amino acid sequence of SEQ ID NO:2 is 100% identical to the present SEQ ID NO:2, and can for hetero- and homodimers. (*See* Office Action at page 3.) The Examiner further asserts that Ferrara teaches "VEGF-E variants including one or more amino acid residues are added, deleted, or substituted at the N- or C-terminus or within the sequence as well as active fragments thereof," and that VEGF-E may be used to stimulate "regrowth of ... connective tissue ..., bone, cartilage ..., and would be useful for indications where angiogenesis is desired such as, among others, osteoporosis ..., and has application in the healing of bone fractures and cartilage damage or defect ...." (*Id.*) The Examiner admits that Ferrara "does not explicitly mention a homodimer of VEGF-E, wherein each chain consisting of residues X-345, and X is an integer from 226-235." The Examiner contends, however, that "it would have been obvious to the person of ordinary skill in the art at the time the invention was made to make the composition comprising the homodimer of the polypeptide fragments as defined in the instant claims ... based on the sequence of VEGF-E taught by Ferrara ...." (*Id.*)

Applicants traverse the instant rejection. For the reasons set forth herein, Ferrara fails to teach or suggest a method as recited in the present claims. As evidence in support of Applicants' remarks, Applicants submit herewith the Declaration of Stephen R. Jaspers under 37 C.F.R. § 1.132 (the "Jaspers Declaration), together with Exhibits A-C, which shows that, as of the application's filing date, a person of ordinary skill in the art reading Ferrara would not have been led to a fragment of human PDGF-C "consisting

of residues X-345 of SEQ ID NO:2, wherein X is an integer from 226 to 235, inclusive," and thus would not have been led to the claimed methods.

First, the legal standard under 35 U.S.C. § 103 is an objective one, in which, "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17, 18 (1966). To establish the *prima facie* case under § 103, the Examiner must show, *inter alia*, some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a reference or combine reference teachings so as to achieve the specific combination as claimed by the applicant. *See* MPEP at §§ 2142 and 2143.01; *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598, 1599 (Fed. Cir. 1988); *In re Dance*, 160 F.3d 1339, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). The suggestion or motivation to modify reference teachings must be found in the prior art and cannot be based on applicant's disclosure. *See* MPEP § 2142; *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). *See also* MPEP §§ 2143 and 2143.01 (citing cases). Moreover, the motivation must be both objective and specific, i.e., the Examiner's showing must be clear and particular. *See In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999).

In the instant case, in view of the state of the art of the PDGF family of growth factors known in the art as of the application's effective filing date (December 7, 1998), a skilled artisan reading Ferrara would not have been specifically led to modify the polypeptide of Ferrara's SEQ ID NO:2 so as to achieve the protein recited in the instant claims, and thus would not have been led to the presently claimed method (*see* Jaspers Declaration at ¶¶ 11-22).

First, Applicants note that PDGF-C has a two-domain structure that, as of the application's effective filing date, was unique among the previously known PDGF family members, PDGF-A and PDGF-B. (Jaspers Declaration at ¶ 11.) In addition to the growth factor domain at the C-terminus (also referred to as the "core PDGF domain"), PDGF-C includes an N-terminal CUB domain (CUB is an abbreviation of C1r/s, Uegf, and bone morphogenic protein-1 [BMP-1]), composed of about 110 amino acids from approximately residues 50 to 160 of the PDGF-C amino acid sequence. The CUB

domain is followed by a hinge region of approximately 80 amino acids in length, linking the CUB domain to the growth factor domain. (*Id.*)

PDGF-C was also unique among PDGFs that were known as of the effective filing date, in that PDGF-C is secreted from cells in a mitogenically inactive form, comprising both the growth factor domain and the CUB domain. (Jaspers Declaration at ¶ 12.) The PDGF-C growth factor domain by itself, in the absence of the CUB domain, is active as a high affinity agonist for PDGF receptor α ("PDGFRα"), while the full-length PDGF-C protein is not. (*Id.* at ¶ 13.) In standard mitogenesis assays, PDGF-C is active only upon cleavage of the CUB domain from the growth factor domain (core PDGF) domain. (*Id.* (citing Li *et al.* [Exhibit B]).) Partial deletion of the N-terminus is inadequate to generate an active fragment of PDGF-C. (Jaspers Declaration at ¶ 13 (citing Fredriksson *et al.* [Exhibit C]).) Even truncated variants of PDGF-C that lack the CUB domain, but retain a significant portion of the hinge region, are inactive. (Jaspers Declaration at ¶ 13 (citing Exhibit C).)

It is further noted that a polypeptide chain as recited in claims 11 and 22 of the application (a polypeptide chain "consisting of residues X-345 of SEQ ID NO:2, wherein X is an integer from 226 to 235, inclusive") corresponds to a bioactive fragment of PDGF-C having the growth factor domain, but lacking the CUB domain and a significant portion of the hinge region. (Jaspers Declaration at ¶ 14 (citing Exhibits B & C).)

With regard to the Examiner's statement that Ferrara teaches "active fragments" of VEGF-E [PDGF-C], Applicants note that the Examiner cites to column 8, lines 15-24 of Ferrara. This cited passage, however, does not teach or suggest any particular active fragments of PDGF-C, nor does this disclosure otherwise provide any specific guidance as to which fragments of PDGF-C would be active. (*See* Jaspers Declaration at ¶¶ 17 & 18.)

Indeed, even when the entire Ferrara disclosure is considered, Ferrara does not teach or suggest, whether explicitly or implicitly, a fragment of PDGF-C as recited in claim 11 or 22 of the application. (Jaspers Declaration at ¶ 19.) Not only does Ferrara fail to teach or suggest a polypeptide fragment comprising the core PDGF-C growth factor domain in the absence of the PDGF-C CUB domain, including a polypeptide chain

"consisting of residues X-345 of SEQ ID NO:2, wherein X is an integer from 226 to 235, inclusive," Ferrara also fails to specifically teach or suggest a unique, two-domain structure for PDGF-C containing an active growth factor domain. (*Id.*) In particular, Ferrara does not teach the approximate boundaries of the growth factor domain of Ferrara's SEQ ID NO:2, nor does Ferrara disclose or suggest that proteolytic cleavage from the inactive precursor of an N-terminal region, comprising the CUB domain and a significant portion of the hinge region, releases the active growth factor domain from the full-length protein. (*Id.*)

Further, with regard to the Examiner's contention that "it would have been obvious to the person of ordinary skill in the art ... to make the ... polypeptide fragments as defined in the instant claims" based on Ferrara's SEQ ID NO:2, Applicants disagree. Contrary to the Examiner's assertion, in view of the state of the art of the PDGF family of growth factors known in the art as the application's filing date, as summarized above, a skilled artisan reading Ferrara would not have been specifically led to modify Ferrara's SEQ ID NO:2 so as to achieve a fragment of PDGF-C as recited in claim 11 or 22 of the application. (Jaspers Declaration at ¶ 21.) Previous to the effective filing date of the instant application, there was no disclosure or suggestion of a PDGF having a two-domain structure as observed for PDGF-C and which is secreted in mitogenically inactive form. (*Id.*) Therefore, as of the application's effective filing date, in view of Ferrara's lack of any teaching or suggestion regarding the two-domain structure of PDGF-C, the significance of this structure with respect to activation, and the absence in the art of other PDGFs having these characteristics, Ferrara would not have specifically suggested to a person of ordinary skill in the art to modify Ferrara's polypeptide of SEQ ID NO:2 to achieve a polypeptide as recited in claim 11 or 22 of the instant application. (*Id.*)

For at least these reasons, because Ferrara does not teach a fragment of PDGF-C as recited in claim 11 or 22, Ferrara also does not teach or suggest a method for using such a PDGF-C fragment as recited in these claims. (Jaspers Declaration at ¶ 22.)

Accordingly, in view of the above, independent claims 11 and 22, and thus all claims depending therefrom, are patentable over Ferrara under 35 U.S.C. § 103. Withdrawal of the present rejection is therefore respectfully requested.

*Ferrara in view of Bentz*

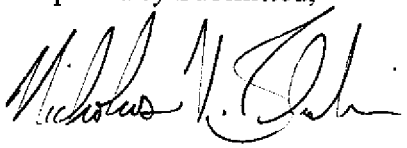
Claims 6 and 24 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ferrara, as applied to claims 2-5, 7-9, 11, 22, 23 and 25, and further in view of Bentz *et al.* (EP 0 512 844 A1).

Applicants respectfully traverse this rejection. As previously set forth, Ferrara does not teach or suggest the use of a fragment of PDGF-C corresponding to the growth factor domain, as required by independent claims 11 and 22. Bentz *et al.* do not cure these deficiencies of Ferrara. Accordingly, claims 6 and 24, which depend directly from claims 11 and 22, are also patentable over the cited art. Withdrawal of the rejection is therefore respectfully requested.

## CONCLUSION

On the basis of the above remarks, Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6558.

Respectfully Submitted,



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Enclosures:
Declaration of Stephen R. Jaspers under 37 C.F.R. § 1.132
(with supporting Exhibits A-C)

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